REMARKS

Reconsideration of the present application in view of the above amendments and following remarks is respectfully requested. As set forth above, Applicant has hereby amended claims 12, 15-17, 19, 21, 23, 27, 36-38, 40, 42, 44, 54, and 56 to more clearly define the subject matter encompassed by Applicant's invention. Support for the claim amendments may be found in the specification as originally filed, in part, at page 5, lines 12-16, and at page 8, lines 18-19. No new matter has been added. Therefore, claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44, and 54-58 are currently pending.

Applicant wishes to thank Examiner Devi for her comments and suggestions during a telephone interview with Applicant's representative on May 15, 2002, to aid in expediting prosecution of the present application in view of the Office Action dated March 26, 2002 (Paper No. 27).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached section is captioned "Version With Markings to Show Changes Made."

APPLICANT'S ARGUMENTS ADDRESSED AS RELEVANT TO THE INSTANT REJECTIONS

In the Office Action dated March 26, 2002, it is acknowledged that Applicant had previously made of record that the terms "immunogenic peptide" and "immunogenic polypeptide" are used interchangeably in the instant specification (*see* response submitted to the U.S. Patent and Trademark Office on November 15, 2001, Paper No. 26). However, it is asserted that the instant specification does not explicitly define the two terms as being synonymous or equivalent. Applicant respectfully disagrees with this assertion as set forth in detail in Paper No. 26. However, as discussed with the Examiner on the telephone and merely to expedite the prosecution of the instant application, Applicant submits that claim terms "immunogenic peptide" and "C-terminal peptide" have been amended to recite "immunogenic polypeptide" and "carboxy-terminal polypeptide," respectively. Applicant further submits that the scope of the amended claims is unchanged by these amendments and is sufficiently clear for a person having

ordinary skill in the art. Accordingly, many of the rejections from the Office Action, which are addressed in turn below, are now moot.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

(a) In the Office Action, claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44 and 54-58 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description. In particular, it is alleged that the specification lacks descriptive support for "immunogenic peptides" in claims 12 and 27, and for "multivalent immunogenic portion" in claims 16 and 37. In addition, it is alleged that the specification lacks descriptive support for a fusion polypeptide having a C-terminal peptide that "is a reiteration of at least one immunogenic peptide from the amino-terminal of the immunogenic portion" of the fusion polypeptide.

Applicant respectfully traverses these grounds of rejection. As noted above, the claim term "peptide" has been amended to recite "polypeptide." Support for "immunogenic polypeptides" and for "carboxy-terminal polypeptides" may be found in the instant specification, for example, at page 2, lines 8-15. Thus, these claim terms are concededly supported by the specification as filed. Furthermore, the claim term "multivalent" has been deleted. Accordingly, Applicant submits that these first two grounds of rejection are now moot and requests that it be withdrawn.

With regard to a carboxy-terminal polypeptide being a "reiteration" of at least one immunogenic peptide from the amino-terminal of the immunogenic portion of the claimed fusion polypeptide, Applicant respectfully submits that this claim limitation is described in the instant specification. As described in the specification and recited in the claims, the instant invention is directed, in pertinent part, to a recombinant fusion polypeptide comprising (a) an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic polypeptides, the polypeptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci and (b) a carboxy-terminal polypeptide that protects the immunogenicity of the immunogenic portion, wherein the carboxy-terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion. As previously made of record, the claimed invention is fully described and supported by the instant specification in, for example, Example 1 (specification at pages 14-16), which teaches

how to make a nucleic acid that encodes an embodiment of the claimed recombinant fusion polypeptide. Example 1 teaches an exemplary fusion polypeptide, comprising M protein fragments (*i.e.*, polypeptides ranging in size from 35 amino acids to 80 amino acids; *see, e.g.*, Figure 7A and B), having a structure of M24-M5-M6-M19-M1-M3-M24 (*see, e.g.*, Figure 7A and B). Thus, in this example, the fusion polypeptide comprises (a) an immunogenic portion having at least two immunogenic polypeptides (here there are six polypeptides derived from the amino-terminal portion of M proteins [M24, M5, M6, M19, M1, and M3], which are each immunogenic as described in Example 3) and (b) a carboxy-terminal polypeptide (M24) that is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion (*see, e.g.*, specification at page 2, lines 8-15; at page 8, line 14-20; at page 16, lines 11-13; at page 20, line 29 through page 21, line 1; and Figure 7A and B).

Hence, Applicant respectfully submits that a carboxy-terminal polypeptide that is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion, as is provided in part by the instant invention, is amply described in the instant specification as filed so as to convey to a person having ordinary skill in the art that Applicant possessed the claimed invention at the time of filing the subject application. Accordingly, Applicant respectfully requests that this rejection be withdrawn.

(b) In the Office Action, claims 16 and 37 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description. In particular, it is alleged that the specification lacks descriptive support for "immunogenic peptides, wherein the peptides are an amino-terminal portion of at least one M protein."

Applicant respectfully traverses this ground of rejection. As set forth above, the claims have been amended to recite "immunogenic polypeptide," which are described in the instant specification, for example, at page 2, lines 8-15. Moreover, the instant specification teaches certain embodiments wherein the immunogenic polypeptides may be from the amino-terminal portion of an M protein (*see, e.g.*, specification at page 5, lines 26-27 and at page 6, line 7). Furthermore, Example 1 and the references cited therein describe how to construct a nucleic acid embodiment having specific 5' regions of different *emm* genes (*see, e.g.*, Example 1 generally and specifically at page 20, lines 6-12) that together encode a fusion polypeptide.

Thus, a person having ordinary skill in the art would understand that the 5' region of an *emm* gene corresponds to the amino-terminal region of a M protein.

Accordingly, a person having ordinary skill in the art would appreciate that Applicant had possession of the claimed invention at the time of filing the subject application. Therefore, Applicant respectfully requests that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

(a) In the Office Action, claims 12 and 27 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, it is allegedly confusing how a carboxy-terminal "immunogenic peptide," which is necessarily immunogenic, is not required to stimulate an immune response in part (b) of claim 12 and part (ii) of claim 27. Furthermore, it is asserted that the scope of claims 12 and 27 are indeterminate because the recitation of "immunogenic peptide" in part (b) of claim 12 and part (ii) of claim 27 lacks antecedent basis and, therefore, need not be one of "the" same immunogenic peptides recited in part (a) of claim 12 and part (i) of claim 27, respectively.

Applicant respectfully traverses these grounds of rejection. Again, as noted above, Applicant respectfully submits that the claims have been amended to recite "immunogenic polypeptide." As described in the specification and recited in the claims, the instant invention is directed, in pertinent part, to a recombinant fusion polypeptide comprising (a) an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic polypeptides, the polypeptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci and (b) a carboxy-terminal polypeptide that protects the immunogenicity of the immunogenic portion, wherein the carboxy-terminal polypeptide is a reiteration of at least one immunogenic polypeptide from the amino-terminal of the immunogenic portion. With regard to immunogenic polypeptides and an immune response elicited therefrom, Applicant respectfully submits that it is not inconsistent for a polypeptide to be immunogenic and at the same time fail to stimulate an immune response because, for example, a carboxy-terminal polypeptide that is a reiteration of at least one immunogenic polypeptide may be degraded or cleaved before an immune response is stimulated (*see, e.g.*, specification at page 8, lines 14-19). Thus, the carboxy-terminal polypeptide may be inconsequential in "stimulating" an immune

response, but may be protective of the recombinant fusion protein having an immunogenic portion (*i.e.*, the immunogenic portion is minimally or not cleaved or degraded due to, for example, the presence of the carboxy-terminal polypeptide) to provide the immunogenic portion an opportunity to stimulate an immune response. However, merely to expedite the prosecution of the instant application, the claim recitation "is not required to stimulate an immune response against Group A Streptococci" has been deleted. Therefore, Applicant submits that "immunogenic polypeptide" as recited in the claims is clear.

Furthermore, Applicant respectfully submits that the recitation of "immunogenic polypeptides" is clear when claims 12 and 27 are read as a whole. These claims clearly define the metes and bounds of all claim terms, including "immunogenic portion," "immunogenic polypeptide," and "carboxy-terminal polypeptide." That is, part (b) of claim 12 should not be read independently of part (a), and similarly part (ii) of claim 27 should not be read independently of part (i). Therefore, Applicant respectfully submits that claims 12 and 27 particularly point out and distinctly claim the invention within the meaning of Section 112, second paragraph.

Accordingly, Applicants respectfully submit that the invention as presently claimed satisfies the requirements of 35 U.S.C. §112, second paragraph, and, therefore, requests that this rejection be withdrawn.

(b) In the Office Action, claims 15-17, 19, 21, 23, 30-32, 34, 36-38, 40, 42, 44 and 54-58 were rejected under 35 U.S.C. §112, second paragraph, as indefinite for the same reasons stated above in part (a). Accordingly, Applicant respectfully requests that this rejection be withdrawn for the reasons set forth above in part (a).

All of the claims pending in the application, claims 12, 15-17, 19, 21, 23, 27, 30-32, 34, 36-38, 40, 42, 44, and 54-58, are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is urged to contact the undersigned attorney if there are any questions prior to allowance of this matter.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC

Jeffrey C. Pepe, Ph.D.
Registration No. 46,985

(JCP:lmp) 284671

Phone: (206) 622-4900
Fax: (206) 682-6031

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 21 of page 16 has been amended as follows:

-- Transformed *E. coli* were grown in a shaking incubator to log phase in 1l of LB containing 100 ~~ug~~μg/ml ampicillin and 25 ~~ug~~μg/ml kanamycin. IPTG (2 mM) was added for the final four hours of growth. The cell pellet was suspended in 30 ml PBS and lysed in a French pressure cell at 1000 psi. The hexavalent protein was purified from the supernatant using Ni-NTA resin according to the protocol provided by the manufacturer (Qiagen, Valencia, CA). The elution buffer containing the protein was concentrated from 15 ml to 5 ml in a spin filter (ULTRAFREE®~~Ultrafree~~-15, Millipore). Final purification was accomplished by gel filtration over SUPERDEX™~~Superdex~~ 75 (prep grade, Pharmacia Biotech). The active fraction was identified by Western blots (Dale, J.B. and Beachey, E.H., "Multiple heart-cross-reactive epitopes of streptococcal M proteins," *J. Exp. Med. 161*:113-122, 1985) using rabbit antiserum against pep M24 (Beachey et al., "Purification and properties of M protein extracted from group A streptococci with pepsin: Covalent structure of the amino terminal region of the type 24 M antigen," *J. Exp. Med. 145*:1469-1483, 1977). Total protein concentration was determined by standard methods and the sample was diluted in PBS to contain 200 ~~ug~~μg/ml of hexavalent protein. Purity of the samples was determined by gel scanning (PHOTOSHOP™~~Photoshop~~ digital image and COLLAGE™~~Collage~~ image analysis).--

Paragraph beginning at line 25 of page 17 has been amended as follows:

-- Two groups of three rabbits each were immunized with 100 ~~ug~~ μg of hexavalent vaccine either precipitated with alum or emulsified in complete Freund's adjuvant. For precipitation in alum, the hexavalent protein (200 ~~ug~~μg/ml) was added to an equal volume of aluminum hydroxide (2 mg/ml) (REHYDRAGEL™ ~~Rehydragel~~ HPA, Reheis, Inc., Berkeley Heights, NJ) and mixed gently at ~~40C~~ 4°C overnight. The hexavalent protein was also emulsified

in CFA at a final concentration of 100 ~~ugμg~~/ml. Rabbits that received the hexavalent vaccine in ~~alum were given 100 ug I.M.~~ μg i.m. as an initial injection and the same dose was repeated at 4, and 8 weeks. The second set of rabbits received 100 ~~ug~~ μgof hexavalent vaccine in CFA subcutaneously as an initial injection and then booster injections of the same dose in saline were given at 4 and 8 weeks. Blood was obtained prior to the first injection and at 2-week intervals thereafter.--

Paragraph beginning at line 14 of page 4 has been amended as follows:

-- ~~Figure 7 is~~ Figures 7A and 7B show a nucleic acid sequence (SEQ ID NO:15) and predicted amino acid sequence (SEQ ID NO:16) of the hexavalent M protein vaccine ~~(SEQ ID NO:15 and SEQ ID NO:16)~~. --

In the Claims:

Claims 12, 15-17, 19, 21, 23, 27, 36-38, 40, 42, 44, 54, and 56 have been amended as follows:

12. (Twice Amended) A recombinant fusion polypeptide, comprising:

(a) ~~a multivalent~~ an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic ~~peptides~~ polypeptides, the ~~peptides~~ polypeptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and

(b) a ~~C terminal peptide which~~ carboxy-terminal polypeptide that protects the immunogenicity of the immunogenic portion, wherein the ~~C terminal peptide~~ carboxy-terminal polypeptide is a reiteration of at least one immunogenic ~~peptide~~ polypeptide from the amino-terminal of the immunogenic portion ~~and is not required to stimulate an immune response against Group A Streptococci~~.

15. (Twice Amended) The polypeptide according to claim 12 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a Group A Streptococci serotype

selected from the group consisting of 1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, ~~52 and 56.~~

16. (Twice Amended) The polypeptide according to claim 12 wherein the immunogenic portion consists of six immunogenic ~~peptides~~ polypeptides, wherein the ~~peptides~~ polypeptides are an amino-terminal portion of at least one M protein.

17. (Twice Amended) The polypeptide according to any one of claims 12 or 15-16 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a serotype 11 Group A Streptococci.

19. (Twice Amended) The polypeptide according to any one of claims 12 or 15-16 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a serotype 13 Group A Streptococci.

21. (Twice Amended) The polypeptide according to any one of claims 12 or 15-16 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a serotype 22 Group A Streptococci.

23. (Twice Amended) The polypeptide according to any one of claims 12 or 15-16 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a serotype 28 Group A Streptococci.

27. (Twice Amended) A composition for promoting an immune response against Group A Streptococci, comprising:

(a) a recombinant fusion polypeptide, comprising:

(i) ~~a multivalent~~ an immunogenic portion wherein the immunogenic portion comprises at least two immunogenic ~~peptides~~ polypeptides, the ~~peptides~~ polypeptides comprising at least 10 amino acids and capable of eliciting an immune response against Group A Streptococci; and

(ii) a ~~C-terminal peptide which~~ carboxy-terminal polypeptide that protects the immunogenicity ~~of the immunogenic portion, wherein the C-terminal peptide~~ carboxy-terminal polypeptide is a reiteration of at least one immunogenic ~~peptide~~ polypeptide from the amino-terminal of the immunogenic portion ~~and is not required to stimulate an immune response against Group A Streptococci~~; and

(b) a pharmaceutically acceptable excipient or diluent.

30. The composition according to claim 27, further comprising an adjuvant.

31. The composition according to claim 30 wherein the adjuvant is alum or Freund's adjuvant.

32. The composition according to any one of claims 27 or 30-31, further comprising an immunomodulatory cofactor.

34. The composition according to claim 32 wherein the immunomodulatory cofactor is selected from the group consisting of IL-4, IL-10, γ-IFN, IL-2, IL-12, and IL-15.

36. (Twice Amended) The composition according to any one of claims 27 or 30-31 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a Group A Streptococci serotype selected from the group consisting of 1, 2, 3, 4, 5, 6, 11, 12, 13, 14, 18, 19, 22, 24, 28, 30, 48, 49, 52 and 56.

37. (Twice Amended) The composition according to any one of claims 27 or 30-31 wherein the immunogenic portion consists of six immunogenic ~~peptides~~ polypeptides, wherein the ~~peptides~~ polypeptides are an amino-terminal portion of at least one M protein.

38. (Twice Amended) The composition according to any one of claims 27 or 30-31 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a serotype 11 Group A Streptococci.

40. (Twice Amended) The composition according to any one of claims 27 or 30-31 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a serotype 13 Group A Streptococci.

42. (Twice Amended) The composition according to any one of claims 27 or 30-31 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a serotype 22 Group A Streptococci.

44. (Twice Amended) The composition according to any one of claims 27 or 30-31 wherein at least one of the immunogenic ~~peptides~~ polypeptides is from a serotype 28 Group A Streptococci.

54. (Amended) The polypeptide according to any one of claims 12 or 27 wherein only one immunogenic ~~peptide~~ polypeptide is reiterated.

55. The polypeptide according to claim 16 wherein each M protein portion is from a different Group A Streptococcal serotype, the serotypes being 1, 3, 5, 6, 19, and 24.

56. (Amended) The polypeptide according to any one of claims 12 or 27 wherein the immunogenic portion consists of ten immunogenic ~~peptides~~ polypeptides, wherein the ~~peptides~~ polypeptides are an amino-terminal portion of a M protein.

57. The polypeptide according to claim 56 wherein each M protein portion is from a different Group A Streptococcal serotype, the serotypes being 1, 3, 5, 6, 18, 19, 22, 24, 28, and 30.

58. The polypeptide according to any one of claims 12 or 27 wherein the immune response against Group A Streptococci comprises the M-protein-specific opsonic antibodies that do not cross-react with human tissue.

284671